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Thrombotic Risk Assessment in Systemic Lupus Erythematosus: validation of the Global Antiphospholipid Syndrome Score (GAPSS) in a prospective cohort

Savino Sciascia[1,2], Maria Jose Cuadrado[3], Giovanni Sanna[3], Veronica Murru[1], Dario Roccatello[2], Munther A Khamashta[1,3], Maria Laura Bertolaccini[1]

[1] Graham Hughes Lupus Research Laboratory, Lupus Research Unit, The Rayne Institute, Division of Women's Health, King's College London, [2] Centro di Ricerche di Immunologia Clinica ed Immunopatologia e Documentazione su Malattie Rare (CMID), Università di Torino, Italy and [3] Louise Coote Lupus Unit, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Correspondence:

Maria Laura Bertolaccini, Graham Hughes Lupus Research Laboratory, Lupus Research Unit, The Rayne Institute, Division of Women's Health, King's College London, 4th Floor Lambeth Wing, St Thomas' Hospital, London SE1 7EH. Tel: +44 02071883569, Fax: +44 02076202658

Mail: maria.bertolaccini@kcl.ac.uk

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Abstract

Objective: This study was performed to prospectively and independently validate the global antiphospholipid syndrome score (GAPSS), a system derived from the combination of independent risk factors for thrombosis, including antiphospholipid antibodies (aPL) and conventional cardiovascular risk factors.

Methods: The GAPSS was applied to 51 consecutive SLE patients, all positive for aPL and prospectively followed up for 32.94±12.06 months. Of them, 48 were female with a mean age of 37.35±12.15 at entry. The GAPSS was calculated yearly for each patient by adding together the points corresponding to the risk factors.

Results: An increase in the GAPSS (entry vs. last visit) was seen in patients who experienced vascular events (n=4, 7.5±4.36 vs. 10.0±5.4, p=0.032). No changes were observed in those without thrombosis (n=47, 8.28±4.88 vs. 7.13±5.75, p= 0.24).

An increase in the GAPSS during the follow up was associated with a higher risk of vascular events (RR 12.30 [95%CI 1.43-106.13, p=0.004), and an increase of more than 3 points showed the best risk accuracy for vascular events (HR 48 [95%CI 6.90-333.85, p=0.0001). The cumulative proportion of thrombosis-free individuals was lower in patients whose GAPSS was increased by 3 or more points (p=0.0027).

Conclusion: We have prospectively demonstrated that GAPSS is a valid tool for accurate prediction of vascular events in SLE patients with aPL.

Significance and Innovation

-Global APS Score (GAPSS) is derived from the combination of independent risk factors for thrombosis and pregnancy loss, taking into account the antiphospholipid antibodies (aPL) profile (criteria and non-criteria aPL), the conventional cardiovascular risk factors, and the autoimmune antibodies profile

-We have prospectively demonstrated that GAPSS is a valid tool for accurate prediction of vascular events in SLE patients with aPL.

Introduction

The antiphospholipid syndrome (APS) is a thrombophilic autoimmune disorder characterised by thrombosis (arterial and/or venous) and/or pregnancy loss, associated with the presence of a specific group of autoantibodies, the so-called antiphospholipid antibodies (aPL). aPL have been demonstrated to be closely associated with thrombotic manifestations,(1) albeit the available studies differ from design, patients selection criteria, aPL profile and associated risk factors.

Whether there are specific serologic or clinical findings that can predict which patients with aPL are most likely to experience a thrombotic event, this is still controversial. While some studies have suggested different antibody profiles, such as simultaneous presence of LAC, aCL, and anti-β2GPI,(2) or LAC, anti-β2GPI and aPS/PT,(3) as identifiers of at-risk status others suggest that clinical characteristics such as hypertension (4) are predictive of risk.

Recently, we conducted a cross-sectional study in a large cohort of well-characterised Systemic Lupus Erythematosus (SLE) patients applying a newly developed risk score for APS (Global APS Score or GAPSS).(5) This score was derived from the combination of independent risk factors for thrombosis and pregnancy loss, taking into account the aPL profile (criteria and non-criteria aPL), the conventional cardiovascular risk factors, and the autoimmune antibodies profile.(5) As a result, we demonstrated that a risk profile could be successfully assessed, suggesting that GAPSS is a potential quantitative predictor of APS-related clinical manifestations risk in SLE.

In the present study, we aimed at prospectively evaluate the clinical relevance of GAPSS in a cohort of SLE patients with aPL but without previous thrombotic events.

Patients and Methods

Patients

This study included 51 consecutive SLE patients. Of them, 48 were female with a mean age 37.35±12.15. All patients attended the Louise Coote Lupus Unit at St Thomas Hospital, London as part of a large, randomized, double blind clinical trial evaluating the efficacy and safety of low dose aspirin (LDA) versus LDA plus low-intensity warfarin in the primary thrombosis prevention in aPL positive patients with SLE (ALIWAPAS).(6)

Inclusion criteria were: a) the presence of aPL (medium or high titers of aCL defined as IgG>20 GPL and/or IgM >20 MPL and/or LA positive) on at least two occasions, with an interval of 6 weeks, during the year previous to the inclusion into the study, b) SLE patients meeting 4 or more ACR criteria for the classification of SLE (7) and c) Age between 18-65 years. Exclusion criteria were: positivity for aPL but without SLE, previous thrombotic events, uncontrolled hypertension, active gastric or duodenal ulcer, severe thrombocytopenia (platelets <50.000mm3), hepatic failure, severe illness i.e. cancer, allergy to aspirin, allergy to warfarin, or being currently pregnant.

The mean follow-up was 32.94±12.06 months. Demographic, clinical and laboratory characteristics are summarised in Table 1.

By the original study design (6), patients had an initial visit to obtain the necessary data for randomization. After being allocated to one of the treatment groups, they had a baseline assessment, followed by six monthly visits. Data regarding conventional risk factors for thrombosis were collected at all visits. All clinical events (notably

thrombotic or hemorrhagic events) were particularly scrutinized with standard methods to objectively document them.

Ethical approval was obtained from the Guy's and St Thomas' Ethics committee and all patients involved in this study gave their written consent.

Assessment of Cardiovascular Risk Factors

Cardiovascular risk factors were assessed following NICE guidelines (8, 9) In detail, enrolled patients underwent at each visit a physical examination, blood pressure determination, and phlebotomy for vascular risk factors according to ALIWAPAS protocol. Arterial hypertension was defined as appropriately sized cut off high blood pressure (140/90 mmHg or higher), at least in two occasions or use of oral anti-hypertensive medications (8). Serum total and HDL cholesterol levels were determined with standardized enzymatic methods and interpreted according to current cut off values (10) (total cholesterol of < 5.0 mmol/l, for LDL cholesterol of < 3.0 mmol/l).

Autoantibodies detection

aPL profile included anticardiolipin antibodies (aCL), lupus anticoagulant (LA), anti-β2glycoprotein-I antibody (anti-β2GPI), and antibodies to phosphatidylserine/prothrombin complex (aPS/PT).

The aCL and anti-β2GPI were detected by ELISA as described previously.(11, 12) Plasma samples were tested for the presence of LA according to the recommended criteria from the ISTH Subcommittee on Lupus Anticoagulant-Phospholipid-dependent antibodies.(13, 14)

The aPS/PT were detected as previously reported. (15, 16) Antinuclear antibodies were measured by indirect immunofluorescence on rodent liver cells, and anti-dsDNA antibodies by radioimmunoassay (Farr assay).

GAPSS calculation

The GAPSS system was calculated for each patient as previously reported, by adding together the points corresponding to the risk factors at each visit.(5, 6) GAPSS was computed on a yearly basis and at the time of the event in patients who developed thrombosis. Assigned points to risk factors based on the linear transformation of the corresponding β regression coefficient were, as previously reported, 3 for hyperlipidemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-β2GPI IgG/IgM, 3 for aPS/PT IgG/IgM and 4 for LA.(5) (Table 2)

Outcome measures

The primary outcome measure for the main trial was thrombosis. As only objectively verified thrombotic events were considered as an end point, accurate investigations were performed in order to document the event, as described in the original publication.(6)

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means ±SD. The significance of baseline differences was determined by the chi-square test, Fisher's exact test, or the unpaired t-test, as appropriate. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Sensitivity and specificity for different cut off values were also

assessed for recurrences. The discriminative ability (ability of the score to classify patients and overall predictive performance for different cut off) of the GAPSS was calculated by measuring the area under the receiver operating characteristic (ROC) curve. The cumulative risk for experiencing the event was estimated by means of the Kaplan–Meier method. The results were presented as hazard ratios with their 95% confidence intervals (HR [95%CI]) and p values. Proportional-hazards regression analysis with the Wald significance test was then used to examine the change in GAPSS and patients characteristics on the risk of developing thrombosis.

All statistical analyses were performed using SPSS 19.0 (Chicago, Illinois, USA).

Results

Overall, baseline GAPSS was 8.21±4.08 [range 3-17].

The primary end point occurred in 4/51 patients from this cohort (7.8%). The incidence of thrombotic events was 2.68 events/100 person-years.

An increase in the GAPSS (entry vs. last visit) was seen in patients who experienced vascular events (n=4, 7.5±4.36 vs. 10.0±5.4, p=0.032). No changes were observed in those without thrombosis (n=47, 8.28±4.88 vs. 7.13±5.75, p= 0.24) (Figure 1.A). When GAPSS values were analysed yearly, an increase was also observed only in patients who developed vascular events when compared to those without (p= 0.0316) (Figure 1.B).

Demographic and clinical characteristics of patients who developed vascular events are summarised in Table 3.

An increase in the GAPSS during the follow up was associated with a higher risk of vascular events (RR 12.30 [95%CI 1.43-106.13, p=0.004). A separate analysis applying an adjusted version of the score which excluded aPS/PT (adjusted GAPSS

or aGAPSS) was performed. In this adjusted form, an increase in the aGAPSS during the follow up was also associated with a higher risk of vascular events (RR 8.60 [95%CI 1.64-88.90, p=0.015).

An increase of more than 3 GAPSS points seemed to have the best risk accuracy for vascular events (HR 48 [95%CI 6.90-333.85, p=0.0001). Consistently, a decrease in the GAPSS was observed in 22 patients: in 8 due to successful treatment of hyperlipidemia and/or arterial hypertension, in 14 due to changes in their aPL profile. None of these patients developed any vascular event.

No changes in SLEDAI (entry vs. last visit) were seen in patients who experienced vascular events (n=4, 1±2 vs. 1.5±3, p=0.79) when compared to those without thrombosis (n=47, 1.6±4.75 vs. 1.9±4.23, p= 0.88).

The risk of thrombosis was also evaluated by Kaplan-Meier analysis. The cumulative proportion of thrombosis-free individuals was lower in patients whose GAPSS was increased by 3 or more points (p=0.0027) (Figure 1.C).

Discussion

This study was aimed at prospectively evaluating the clinical relevance of GAPSS in predicting the risk of thrombotic event in a cohort of 51 SLE patients from a single center, prospectively followed up as part of a larger RTC.(6)

In this study, we showed that an increase in the GAPSS during the follow up is seen in those SLE patients who experienced vascular events when compared to those who did not experience such an event. Recent studies have suggested that different aPL profiles are able to identify patients at a higher risk of thrombosis. Patients with “triple postivity” for aCL, anti-β2GPI and LA,(2) and those with anti-β2GPI, aPS/PT and LA,(3) have been shown to be at a higher risk of developing thromboembolic

events. Moreover, conventional cardiovascular risk factors have been proved to strongly contribute to the development of thrombosis in APS. An early prospective study of 404 subjects, 226 with APS and 178 asymptomatic carriers of aPL, found that 50% of patients with APS had coincident risk factors for arterial thrombosis, such as hypercholesterolemia and arterial hypertension, at the time of the first thrombotic event.(17) A recent prospective study in 258 aPL carriers showed that hypertension and LA were significantly predictive of the first thrombotic event.(4) Moreover, hypertension and LA were identified by multivariate logistic regression analysis as independent risk factors for thrombosis in this cohort (4) and others.(5)

Our data indicate that the combination of certain aPL tests along with conventional cardiovascular risk factors should be considered when assessing the risk of thrombosis. A profile including hyperlipidemia, arterial hypertension, aCL anti-β2GPI, aPS/PT and LA form the bases for the GAPSS. In our study, patients who experienced an increase in GAPSS of more or equal than 3 during the follow-up had a 48-times increased risk to develop a thrombotic event.

In this setting, the GAPSS represents an important tool allowing for a substantial improvement in quantifying the risk to develop thrombosis.

We accept that this approach has some limitations. Firstly, patients were randomized for LDA vs. LDA+ low-intensity warfarin in the original study, a trial on primary thromboprophylaxis designed back in 1998.(6) In the main ALIWAPAS trial, LDA+ low-intensity warfarin did not result in a significant reduction in thrombotic event rate. When adjusted for the treatment regimen, we also observed no differences in thrombotic incidence in patients treated with in LDA vs LDA+ low-intensity warfarin in this subgroup.We acknowledge that this therapeutic approach is not currently adopted in the clinical practice anymore; however, as the original trial failed in

observing a significant difference in thrombotic event rate in the two arms, we feel that this did not significantly impact on the validation of GAPSS in this study. In addition, the ALIWAPAS trial recruitment was based on the Sapporo criteria (18). However, no anti-β2GPI antibodies alone are seen our experience, therefore this should not limit our data (3).

Second, the effect of targeted therapy for hypertension and/or hyperlipidemia, both significant variables when evaluating risk, could not be assessed, as treatment varied according to the clinical manifestations and clinician judgement. However, no patient who experienced a decrease in the GAPSS value (8 out of 51 patients) due to a better control of co-morbilites experienced a thrombotic event, supporting the concept that an effective control of conventional risk factors could reduce the risk of developing future events.

Third, cases of aPL levels fluctuation and conversion from positive to negative have been reported. Changes in the score may be due to aPL profile change and to a better/worse control of other risk factors (19, 20). Indeed, aPL titers fluctuation can be observed in the routine clinical practise and its clinical significance is still under debate.

Fourth, disease activity has been shown as an important determinant in the occurrence of thrombotic events in SLE patients (21). However, in this study, no changes in SLEDAI (entry vs. last visit) were seen in patients who experienced vascular events when compared to those without thrombosis. Moreover, also when adjusted for the immunosuppressive regimen, we observed no differences in thrombotic incidence in patients with or without immunosuppressant agents.

Finally, we reported two events as transient ischemic attacks, defined according to National Institute of Neurological Disorders and Stroke.(22) In both the cases hyperintensity lesions compatible with small vessels ischemia were found at MRI.

In summary, in this study we validated the GAPSS in a prospective cohort as a valid tool for risk stratification for thrombosis. Such an approach on the categorization of APS patients based upon a quantitative score may, in the future, influence the clinical judgment and therapeutic approach.

LEGEND

Figure 1.

A. Distribution of GAPSS (entry vs. last visit) according to clinical manifestations. Data are shown as box plots, where each box represents the 25th to 75th percentiles: lines inside the box represent the median. The whiskers represent the 95%CI. Higher values of GAPSS were seen in patients who developed vascular events (VE+ve) when compared to those without (VE-ve).

B. Distribution of GAPSS analysed yearly according to clinical manifestations. Data are shown as box plots, where each box represents the 25th to 75th percentiles: lines inside the box represent the median. The whiskers represent the 95%CI. Higher values of GAPSS were seen in patients who developed vascular events (VE+ve) when compared to those without (VE-ve).

C. Kaplan-Meier analysis of the risk of vascular event. The cumulative proportion of thrombosis-free individuals was lower in patients whose GAPSS was increased by 3 or more points (Delta ≥ 3).

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